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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/808,541 | 03/25/2004 | Abraham Nudelman | 27755 | 4875 |

7590 02/01/2007

Martin D. Moynihan
PRTSI, Inc.
P. O. Box 16446
Arlington, VA 22215

| EXAMINER | |
|---|---|
| COLEMAN, BRENDA LIBBY | |
| **ART UNIT** | **PAPER NUMBER** |
| 1624 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 02/01/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

# Office Action Summary

| Application No. | Applicant(s) | |
|---|---|---|
| 10/808,541 | NUDELMAN ET AL. | |
| **Examiner** | **Art Unit** | |
| Brenda L. Coleman | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *12-14,16-25,35-37,54-56,72-74,97,99-116 and 127* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-4,7,8,10,12-27,30,31,33,35-39,42-45,49,50,52,54-59,61-64,67,68,70,72-75,93-119 and 124-131.

Continuation of Disposition of Claims: Claims rejected are 1-4,7,8,10,15,26,27,30,31,33,38,39,42-45,49,50,52,57-59,61-64,67,68,70,75, 93-96,98,117-119, 124-126 and 128-131.

## DETAILED ACTION

Claims 1-4, 7, 8, 10, 12-27, 30, 31, 33, 35-39, 42-45, 49, 50, 52, 54-59, 61-64, 67, 68, 70, 72-75, 93-119 and 124-131 are pending in the application.

This action is in response to applicant's amendment filed November 15, 2006. Claim 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 44, 45, 49, 50, 52, 57-59, 61-63, 67, 68, 70, 75, 93-95, 98, 117-119, 124 and 125 were amended, claims 5, 6, 9, 11, 28, 29, 32, 34, 40, 41, 46-48, 51, 53, 60, 65, 66, 69, 71, 76-92 and 120-123 were cancelled and claims 126-131 are newly added.

### *Response to Amendment*

Applicant's arguments filed November 15, 2006 have been fully considered with the following effect:

1. With regards to the 35 U.S.C. § 112, first paragraph rejection labeled paragraph 5) of the last office action, the applicant's amendments and remarks have been fully considered but they are not persuasive. The applicants' stated that "since the preparation of the conjugates described in the instant application is based on reacting a carboxylic acid group of an organic acid (the second moiety) with a suitable (e.g. amine, hydroxyl or thiol) functional group of a psychotropic drug, to thereby form, via a simple nucleophilic-addition reaction, a corresponding ester bond between these groups, and further since such addition reactions of carboxylic acid groups are simple, widely recognized and well-explored reactions, the specification of the instant application, by showing the feasibility to provide nine exemplary conjugate, provides a reasonable enablement for preparing the conjugates embraced by the instant application". As

stated in prior office actions the nature of the invention in the instant case, has claims, which embrace chemical conjugates, which contain a phenothiazine core, which are coupled together with a second chemical moiety of which the number and nature of the organic acid moieties are extensive and complex. However, the reaction between a phenothiazine having a free amine, hydroxyl, or thiol group and free carboxylic group before being conjugated to said first chemical moiety is not described in the specification.

In view of the lack of direction provided in the specification regarding starting materials, the lack of working examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The applicants' are not entitled to preempt the efforts of others. The test for determining compliance with 35 U.S.C. § 112 is whether the applicants have clearly defined "their" invention not what may be discovered by future research.

Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the species in the specification of examples AN-130, AN-167, AN-168, AN-177, AN-178, AN-180, AN-179, AN-181, AN-187 and AN-216, does not reasonably provide enablement for the compounds, compositions, method of use and process of preparing

the compounds as claimed herein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for reasons of record and stated above.

2. The applicant's amendments and arguments are sufficient to overcome the 35 U.S.C. § 112, second paragraph rejection labeled paragraph 6c), e), f), h), i), j), k), l), o), p), q), r), s) and t) of the last office action, which are hereby **withdrawn**. However with regards to the 35 U.S.C. § 112, second paragraph rejections labeled paragraph 6a), b), d), g), m) and n) the applicant's amendments and remarks have been fully considered but they are not persuasive.

a) The applicants' state that claim 1 has been amended to no longer include the phrase "psychotropic drug residue" but instead interchangeably, the phrases "a residue of a psychotropic drug". As the applicants' have stated the amendment to the phrase is interchangeably and thus does not further exemplify what the applicants mean by a residue of a psychotropic drug. Residue is a broad term, which does not define what else is attached to the psychotropic drug.

Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

b) The applicants' state that the phrase "organic acid" has a clear meaning and is unambiguous interpreted by any person skilled in the art, and further strongly believes that the definitions and description set forth hereinabove even more clearly define both the phrase "organic acid" and the phrase "organic acid residue". However, the phrase organic acid can be more than that which is exemplified by the applicants', i.e. organic acid is more than just -C(O)OH and organic acid residue is more than just R-C(=O)-O- or R-C(=O)-. An "organic acid" is an organic compound with acidic properties with the most common organic acids being carboxylic acids whose acidity is associated with their carboxyl group –COOH and sulfonic acids, containing the group $OSO_3H$. Residue is a broad term, which does not define what else is attached to the organic acid.

Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

d) The applicants' state that the phrase "GABA agonist residue" is well defined in the instant application and that claims 2, 44, 62, 94, 117 and 199 have been amended to recite instead the phrase "γ-aminobutyric acid residue". Residue is a broad term, which does not define what else is attached to the γ-aminobutyric acid.

Claims 2, 44, 62, 94, 117 and 119 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

g) The applicants' state that the phrase "anti-proliferative activity" is a widely recognized term, which is widely cited in publications, patents and patent applications worldwide. The rejection of claims 4, 27 and 64 was on the grounds that it is indefinite, in that it is not known which diseases are capable of being responsive to anti-proliferative activity. The scope of diseases and/or disorders associated with anti-proliferative activity could alter over time. The applicants' are not entitled to preempt the efforts of others. Claims 4, 27 and 64 do not set forth the metes and bounds of these claims.

Claims 4, 27 and 64 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

m) The applicants' state that claims 11, 34, 53, 71, 88 and 119 have been canceled however, claim 119 has not been canceled.

Claim 119 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicants regards as the invention, for reasons of record and stated above.

n) The applicants' state that the "since butyric acid, valeric acid, 4-phenylbutyric acid, and 4-aminobutyric acid are known compounds" applicants' believe that the metes and bounds of claims 15, 38, 57, 75, 92 and 125 are set forth. Residue is a broad term, which does not define what else is attached to the butyric acid, valeric acid, 4-phenylbutyric acid and 4-aminobutyric acid.

Claims 15, 38, 57, 75 and 125 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention, for reasons of record and stated above.

3. The applicant's amendments and arguments are sufficient to overcome the 35 U.S.C. § 102, anticipation rejection labeled paragraph 7) of the last office action, which is hereby **withdrawn.**

In view of the amendment dated November 15, 2006, the following new grounds of rejection apply:

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to claim 1 where claim 1 states "said psychotropic drug being a phenothiazine, said phenothiazine having a free amine, hydroxy, or thiol group before being conjugated to said second chemical moiety" and further wherein said second chemical moiety is a residue of an organic acid, "said organic acid having 3-5 carbon atoms in its backbone chain and further having a free carboxylic group before being conjugated to said first chemical moiety, whereas said residue of said phenothiazine is a portion of said phenothiazine that is formed upon reacting said amine, hydroxy or thiol group of said phenothiazine and said carboxylic group of said organic acid, and further whereas said residue of said organic acid is a portion of said organic acid that is formed upon reacting said carboxylic group with said amine, hydroxyl, or thiol group of said phenothiazine" is not described in the specification with respect to the genus.

5. Claims 58, 59, 61-64, 67, 68, 70 and 75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of the method

claims is not adequately enabled solely based on the GABA agonist activity provided in the specification. The specification, while being enabling for the treatment of schizophrenia, does not reasonably provide enablement for treatment of all the disorders claimed herein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In addition to other disorders, which are difficult to treat these claims call for the treatment of cancer, which are capable of being modulated by inhibiting an activity of GABA. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to treat cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective anti-tumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure. Genentech Inc. v. Novo Nordisk 42 USPQ2d 1001.

6. Claim 98 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amendment to claim 98 where claim 98 states "acyl" which is not described in the specification with respect to the genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 126 and 178-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reason(s) apply:

a) Claims 126 and 128-131 are vague and indefinite in that it is not known what is meant by perphenazine residue. Residue is a broad term, which does not define what else is attached to the perphenazine.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57, 93-96, 98, 117-119, 124-126, 128, 130 and 131 are rejected under 35 U.S.C. 102(b) as being anticipated by Craig, U.S. Patent No. 2,914,528. U.S. '528 teaches the compounds, compositions, process of preparing and method of use of the compounds of formula I where A is $-(CH_2)_3-$; $SO_2CF_3$ is bound in the 2 position of the phenothiazine ring; $R_1$ and $R_2$ together with the nitrogen to which they are attached form a piperazinyl ring substituted by N-(ω-alkanoyloxyalkylene) such as $-(CH_2)_4O-C(=O)-CH_2CH_2CH_3$ as set forth in example 24.

9. Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith Kline & French Laboratories, GB Patent No. 829,246. GB '246 teaches the compounds, compositions and method of use of the compounds of formula I where A is $-(CH_2)_3-$; Y is $CF_3$; $R_6$ is $-(CH_2)_4O-C(=O)-CH_2CH_2CH_3$, $-(CH_2)_2O-C(=O)-CH_2CH_3$, $-(CH_2)_2O-C(=O)-CH_2Cl$, $-(CH_2)_2O-C(=O)-CH_2CH_2CHMe_2$, $-(CH_2)_2O-C(=O)-CH=CH-CH_3$, $-(CH_2)_2O-C(=O)-O-CH_2CH_2Cl$, etc. as set forth in example 5, 17, etc.

10. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57, 93-96, 98, 117-119, 124-126, 128, 130 and 131 are rejected under 35 U.S.C. 102(b) as being anticipated by Edgerton, U.S. Patent No. 2,944,053. U.S. '053 teaches the compounds,

compositions and method of use of the compounds of formula I where A is $-(CH_2)_3-$; Y is $COCF_3$; $R_1$ and $R_2$ together with the nitrogen to which they are attached form a piperazinyl ring substituted by N-(ω-alkanoyloxyalkylene) or N-(ω-alkanoyloxyalkyleneoxyalkylene) such as $-(CH_2)_4-O-(CH_2)_4-O-C(=O)-CH_2CH_2CH_3$ or $-(CH_2)_2-O-C(=O)-CH_2CH_3$ as set forth in examples 5, 11, etc.

11. Claims 1-3, 7, 8, 10, 15, 26, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57, 93-96, 98, 117-119, 124-126, 128, 130 and 131 are rejected under 35 U.S.C. 102(b) as being anticipated by Cusic, U.S. Patent No. 2,969,358. U.S. '358 teaches the compounds, compositions and method of use of the compounds of formula I where R is $-(CH_2)_3-O-C(=O)-CH_2CH_3$ as set forth in column 6.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

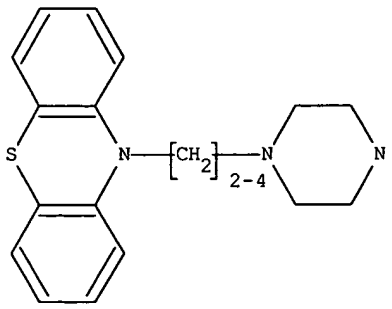
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-4, 7, 8, 10, 15, 26, 27, 30, 31, 33, 38, 39, 42-45, 49, 50, 52, 57-59, 61-64, 67, 68, 70, 75, 93-96, 98, 117-119, 124-126 and 128-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith Kline & French Laboratories, GB 829,246. The generic structure of GB 829,246 encompasses the instantly claimed compounds (see Formula I, page 2) as claimed herein. Examples 5, 17, etc. which anticipate the claims herein as set forth above may differ in nature of the A, Y, $R_1$, $R_2$,

$R_3$, $R_4$, $R_5$ and $R_6$ substituents. Page 1, line 37 through page 2, line 50 define the substituents as follows: Y represents perfluoroalkyl of 1 to 3 carbon atoms, preferably –$CF_3$; A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms; $R_1$ is H; $R_2$, $R_3$, $R_4$ and $R_5$ each represent methyl, ethyl or hydrogen; $R_6$ represent the following:.....aliphatic-acyloxy-lower alkyl having from 1 to 6, preferably 2 to 4 carbon atoms in the acyloxy portion and 2 to 6 carbon atoms in the lower alkyl portion, such as acetoxyethyl, crotonoyloxyethyl, butyryloxybutyl or isocaproyloxyethyl,.... The compounds of the instant invention are generically embraced by GB '246 in view of the interchangeability of the substitutions of the phenothiazine ring system. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example crotonoyloxybutyl for $R_6$ as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

***Election/Restrictions***

13. The Applicants' are reminded that the compounds of claim 1 have only been examined to the extent that the species contain the perphenazine core, i.e.



14. Claims 12-14, 16-25, 35-37, 54-56, 72-74, 97, 99-116 and 127 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 1, 2006.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brenda Coleman

Brenda L. Coleman
Primary Examiner Art Unit 1624
January 30, 2007

**PTO/SB/08a (08-03)**
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE





Substitute for form 1449A/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*

| *Complete if Known* | |
|---|---|
| Application Number | 10/808,541 |
| Filing Date | March 25, 2004 |
| First Named Inventor | Abraham NUDELMAN et al. |
| Art Unit | 1624 |
| Examiner Name | COLEMAN, Brenda Libby |
| Attorney Docket Number | 27755 |

Sheet 1 of 3

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear<br>class | <br>subclass |
|---|---|---|---|---|---|---|
| BC | 1 | US-3,966,930 | 06-29-1976 | Buus et al. | 514 | 225.8 |
| BC | 2 | US-5,994,392 | 11-30-1999 | Shashoua et al. | 514 | 437 |
| BC | 3 | US-5,525,727 | 06-11-1996 | Bodor et al. | 546 | 39 |
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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Documents<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| BC | 4 | PCT WO 02/43652 | 06-6-2002 | Gil-Ad et al. | | |
| BC | 5 | PCT WO 03/026563 | 03-3-2003 | Nudelman et al. | | |
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| Examiner Signature | Brenda Coleman | Date Considered | Jan. 29, 2007 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (08-03)
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# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

*(use as many sheets as necessary)*

| Complete if Known | |
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| Application Number | 10/808,541 |
| Filing Date | March 25, 2004 |
| First Named Inventor | Abraham NUDELMAN et al |
| Group Art Unit | 1624 |
| Examiner Name | COLEMAN, Brenda Libby |
| Attorney Docket Number | 27755 |

Sheet 2 of 3

| Examiner Initials | Cite No.[1] | OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS<br>Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published. | T[2] |
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| | | | |

| Signature | Brenda Coleman | Considered | Jan. 29, 2007 |
|---|---|---|---|

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| BC | 20 | Pouzet et al. "Effects of the 5-HT7 Receptor Antagonist SB-258741 in Animal Models for Schizophrenia", Pharmacology, Biochemistry and Behavior, 71: 655-665, 2002. | |
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| Notice of References Cited | Application/Control No. 10/808,541 | Applicant(s)/Patent Under Reexamination NUDELMAN ET AL. | |
|---|---|---|---|
| | Examiner Brenda L. Coleman | Art Unit 1624 | Page 1 of 1 |

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| * | C | US-2,969,358 | 01-1961 | CUSIC JOHN W | 544/45 |
| | D | US- | | | |
| | E | US- | | | |
| | F | US- | | | |
| | G | US- | | | |
| | H | US- | | | |
| | I | US- | | | |
| | J | US- | | | |
| | K | US- | | | |
| | L | US- | | | |
| | M | US- | | | |

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**NON-PATENT DOCUMENTS**

| * | | Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages) |
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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Brenda Coleman Jan 30, 2007

AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner acting for the Comptroller-General dated the twenty-sixth day of April, 1961, under Section 29, of the Patents Act, 1949. Reference has also been directed in pursuance of Sections 8 and 9 of the Act.

# PATENT SPECIFICATION

NO DRAWINGS

**829,246**

*Date of Application and filing Complete Specification: Oct. 21, 1957.*

*No. 32856/57.*

*Application made in United States of America on May 13, 1957.*

*Complete Specification Published: March 2, 1960.*

**Index at acceptance:—Class 2(3), C1C(1B:2:3:4:8:9:10:11E:11F:11G:11J), C1E(2K4:3K4), C1F1(B:D3), C3A12(A4A:B3:C6), V.**

**International Classification:—C07d.**

COMPLETE SPECIFICATION

## Improvements in or relating to New Perfluoroalkylphenothiazine Derivatives

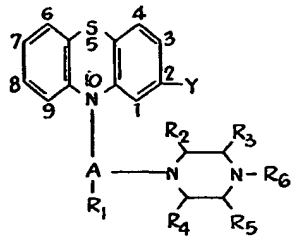
We, SMITH KLINE & FRENCH LABORATORIES, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, of 1530 Spring Garden Street, City of Philadelphia, Commonwealth of Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is performed, to be particularly described in and by the following statement:—

This invention relates to new 10-(piperazinylalkyl) - perfluoroalkylphenothiazine derivatives. The novel compounds of this invention are of value as therapeutic agents.

More specifically, the compounds of this invention have utility as antiemetics, tranquilizers, antihistaminics, spasmolytics, antishock agents and potentiators of various drugs such as analgetics and anesthetics. When used as tranquilizers, these compounds have the ability to abate mental disturbances such as anxiety, confusion or excitation without physical incapacitation. In addition, these compounds have chemotherapeutic or antimicrobial activity, such as antibacterial and fungicidal activity. Further, the novel compounds of this invention have a surprisingly low degree of toxicity.

The compounds of this invention are 10-(piperazinylalkyl) - perfluoroalkylphenothiazine derivatives represented by the general formula:

FORMULA I.



wherein:

Y represents perfluoroalkyl of 1 to 3 carbon atoms, preferably —$CF_3$,

A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms,

$R_1$ is H,

$R_2$, $R_3$, $R_4$ and $R_5$ each represent methyl, ethyl or hydrogen,

$R_6$ represents the following:

*cycloalkyl* of 5 or 6 carbon atoms, for example, cyclopentyl and cyclohexyl;

*cycloalkylalkyl* of from 6 to 10 carbon atoms, such as β-cyclohexylethyl and β-cyclopentylmethyl;

*alkenyl* of from 2 to 6 carbon atoms such as allyl and isocrotonyl;

*dialkylamino - lower - alkyl* having one to six carbon atoms in each of the alkyl por-

tions and 2 to 6 carbon atoms in the lower alkyl portion, preferably dimethyl or diethylamino-lower-alkyl, for example dimethylaminobutyl and diethylaminoethyl;

*hydroxy - lower - alkyl* of from 2 to 6 carbon atoms, for example, hydroxyethyl and hydroxybutyl;

*hydroxy - lower - alkyl - oxy - lower - alkyl*, the lower alkyl portions having 2 to 6 carbon atoms, for example, ω-hydroxyethoxyethyl and ω-hydroxypropoxypropyl;

*phenyl; cinnamyl; furoyloxybutyl; furoyl; thenyl;*

*monocyclic aralkyl* having 2 to 6 carbon atoms in the alkyl portion, for example, *phenyl-lower*-alkyl, such as benzyl, phenethyl and ω-phenylbutyl;

*aliphatic acyl* of from 1 to 6, preferably 1 to 4 carbon atoms, for example, formyl, acetyl, butyryl, propionyl, caproyl, isocaproyl, or crotonyl or halogenated derivatives of said aliphatic acyls such as chloroacetyl, trifluoroacetyl, heptafluorobutyryl and dichloroacetyl; *alicyclic aliphatic acyl of from 7 to 10 carbon atoms*, such as cyclopentylpropionyl, hexahydrobenzoyl and cyclohexylbutyryl; *monocyclic aryl-aliphatic acyl of from 6 to10 carbons*, such as cinnamoyl, phenylacetyl, phenylpropionyl or benzoyl; *carbomethoxy; carbethoxy; carbobenzoxy; carbamyl;*

*dialkyl carbamyl* having 1 to 6 carbon atoms in the alkyl portions such as diethylcarbamyl or dimethylcarbamyl; *N-phenyl carbamyl;*

*aliphatic - acyloxy - lower - alkyl* having from 1 to 6, preferably from 2 to 4 carbon atoms in the acyloxy portion and 2 to 6 carbon atoms in the lower alkyl portion, such as acetoxyethyl, crotonoyloxyethyl, butyryloxybutyl or isocaproyloxyethyl and *monocyclic aroyloxy - lower - alkyl* having 2 to 6 carbon atoms in the lower alkyl portion such as benzoyloxy-lower-alkyl. Any of the acyl moieties defined above under "acyl" can be used as substituents on the oxygen atom of the hydroxy-lower-alkyl moieties.

The values of Y, A, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ in Formula I should be chosen so that in any one compound, when Y is $CF_3$, A is propylene and $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ are each hydrogen, $R_6$ is not hydroxy-lower-alkyl having 2 or 3 carbon atoms in the alkyl portion, nor aliphatic acyloxy-lower-alkyl having 1 to 6 carbon atoms in the acyloxy portion and 2 or 3 carbon atoms in the lower alkyl portion.

Advantageous compounds of this invention are represented by the above structural formula when:

Y repreesnts trifluoromethyl,

A represents ethylene, propylene or 2-methyl-propylene,

$R_2$, $R_3$, $R_4$ and $R_5$ represent hydrogen, and

$R_6$ represents hydroxy - lower - alkyl, aliphatic acyloxy - lower - alkyl or hydroxy-lower - alkyl - oxy - lower alkyl. When A represents ethylene or 2-methylpropylene, and hydroxyl - lower - alkyl having 4 to 6 carbon atoms in the alkyl portion, aliphatic acyloxy-lower-alkyl having 1 to 6 carbon atoms in the acyloxy portion and 4 to 6 carbon atoms in the lower alkyl portion, or hydroxy-lower-alkyl-oxy-lower-alkyl, when A represents propylene.

By the term "alkyl" where used herein, aliphatic groups having not more than 6 carbon atoms and, preferably not more than 4 carbon atoms, is intended except where otherwise specifically indicated.

The term "lower alkyl" is used in connection with alkylene residues and as thus used represents aliphatic groups of from 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms except where otherwise specifically indicated.

This invention also includes salts of the above defined bases formed with non-toxic organic and inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in water-miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or an excess of the acid in water-immiscible solvent, such as ethyl ether or chloroform, with the desired salt separating directly. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, *p*-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids as well as with the 8-halotheophyllines, for example, 8-chlorotheophylline and 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts which is well known to the art.

The compounds of this invention are prepared using 2 - perfluoroalkylphenothiazine starting materials which are prepared by methods well-known to the art and most readily by classical methods of phenothiazine formation, such as thionation of properly substituted 2-perfluoroalkyldiphenyl amines, namely, the Bernthsen reaction. Reference may be had to "S. P. Massie, Chemical Reviews, 54; 794 (1954)".

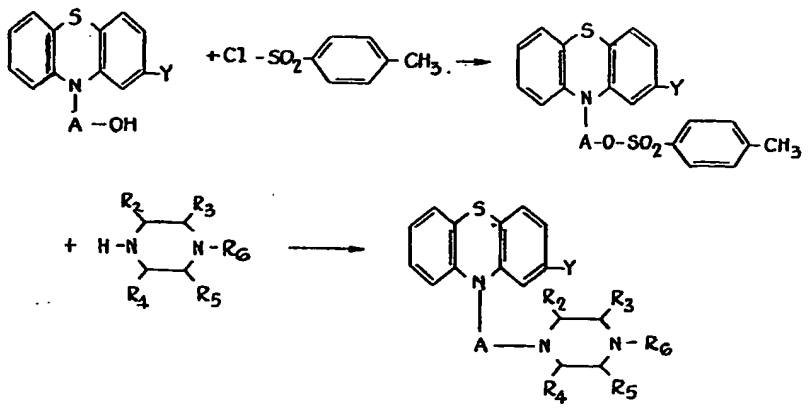
The 2 - perfluoroalkylphenothiazine nucleus is condensed with a reactive piperazinylalkyl ester having the desired piperazinylalkyl group. The condensation is carried out by refluxing the reactants in an inert aromatic solvent, such as benzene, xylene or toluene, in which at least

one of the reactants must be soluble. A suitable acid-binding agent may be included, such as an alkali metal amide, preferably sodium amide or potassium amide; an alkali metal hydroxide, preferably potassium hydroxide; an alkali metal hydride, preferably sodium hydride; or alkali metal aryl or alkyl compounds, preferably phenyl sodium.

The piperazinylalkyl ester is preferably used as the free base although the acid addition salts may be used with a corresponding increase in the amount of inorganic base as defined above. Any reactive piperazinylalkyl ester containing the desired substituted piperazinylalkyl group may be used, such as the halides, preferably bromide or chloride, or the sulfonic or sulfuric esters, preferably the *p*-toluene sulfonate.

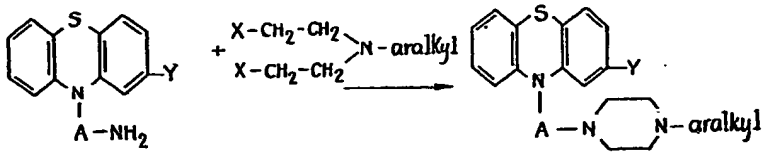
The 10 - (piperazinylalkyl) - perfluoroalkylphenothiazines are alternatively prepared by methods which involve chemical modifications of an alkyl chain which has a reactive, terminal group such as a halogen, a carboxy, tosylate, aldehydo or cyano group and which is attached to the 10-position of the parent 2-perfluoroalkylphenothiazine. Such methods are conveniently used to prepare 10 - (N - substituted-piperazinylalkyl) - 2 - perfluoroalkylphenothiazines and are particularly valuable for the preparation of the piperazines unsubstituted at the terminal N position which are useful intermediates for the preparation of the compounds of this invention. These synthetic procedures will be more evident from the following description.

For example, the 2 - perfluoroalkylphenothiazines substituted in the 10-position with an alkyl chain containing a terminal reactive ester group, such as tosylate, are prepared as in the following procedure. A 2-tetrahydropyranyl ether of a haloalkanol is condensed in an inert solvent, such as xylene, with a 2-perfluoroalkylphenothiazine in the presence of an acid binder, such as sodamide, to give a 10-(ω - tetrahydropyranyloxy - alkyl) - 2 - perfluoroalkylphenothiazine. The protective pyranyl group is removed with acid, for example, hydrochloric acid. The resulting 10-(ω - hydroxyalkyl) - 2 - perfluoroalkylphenothiazine derivatives is then esterified with an appropriate acyl halide, such as tosyl (*p*-toluene sulfonyl) chloride to give the desired reactive ester, in this case the tosylate. The resulting ester is reacted with a piperazine, preferably at reflux in alcohol with a mild alkali. This procedure is illustrated in the following scheme:



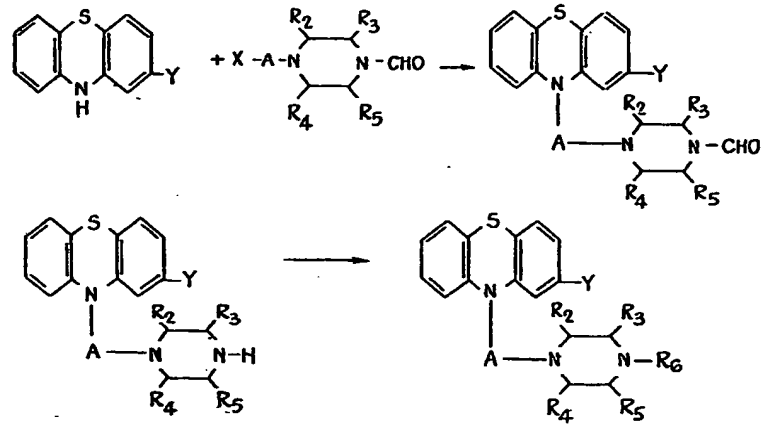
It is, at times, convenient to react the 10-(ω - hydroxyalkyl) - perfluoroalkylphenothiazine derivative obtained as hereafter described with a reactive inorganic halide, such as thionyl chloride, thionyl bromide or phosphorus pentachloride, in a non-ionic solvent, such as benzene or xylene, to give a 10 - (ω - haloalkyl) - perfluoroalkylphenothiazine which is then reacted with a piperizine preferably in excess or in the presence of an acid binder, such as sodium carbonate in an aqueous alcohol medium.

As a further example of the preparation of these compounds, certain 10 - (ω - piperazinylalkyl) - 2 - perfluoroalkylphenothiazine derivatives are prepared from the terminal primary amine derivatives by condensing a 10-(ω-aminoalkyl) - 2 - perfluoroalkylphenothiazine (made readily by reduction of the ω-cyanoalkyl analogue) with a substituted bis - (β-haloalkyl) - amine, such as an aralkylbis - (β-haloalkyl) - amine, to give a 10 - [ω - (N-substituted - piperazinyl) - alkyl] - perfluoroalkylphenothiazine such as a 10 - [ω - (N-aralkylpiperazinyl) - alkyl] - perfluoroalkylphenothiazine as specifically illustrated in the following scheme showing the formation of the N-aralkylpiperazinyl derivatives.



X as used in the above and following scheme equals halogen.

The compounds of Formula I where $R_6$ is an easily removed group such as an acyl group are useful intermediates for preparing other N-substituted compounds of this invention by hydrolysis followed by reaction with reactive esters such as bromides, iodide or chlorides or with ethylene oxide. This route of synthesis conveniently gives compounds of this invention in good yield and purity which would be obtained otherwise with more difficulty. For example, the production of 10 - (N - substituted - piperazinylalkyl) - 2 - perfluoroalkylphenothiazines may be accomplished by protecting the nitrogen of the piperazinylalkyl ester with a formyl group by the following procedure:



The monosubstituted piperazine is heated at reflux with an excess of a formic acid ester, such as methyl or ethyl formate. The volatiles are removed *in vacuo* and the desired N-formylpiperazinylalkyl ester isolated by distillation or fractional crystallization. Optionally, the N-formylpiperazinylalkyl ester may be formed by reversing the order of reaction, for instance by N - formulating ω - hydroxy-lower - alkylpiperazine and then reacting with thionyl chloride to form N - (ω - chloro-lower - alkyl) - N - formylpiperazine. This N-formyl ester is reacted with 2 - perfluoroalkylphenothiazine to give 10-[ω-(N-formylpiperazinyl) - alkyl] - 2 - perfluoroalkylphenothiazine. The protective formyl group is removed by mild hydrolysis conditions, such as with dilute sodium hydroxide solution, to give the desired 10 - (ω - piperazinylalkyl) - 2-perfluoroalkylphenothiazine. Alternatively, the protecting group may be a benzyl group which cannot be removed by hydrolysis but will be removed by catalytic hydrogenation.

This compound is further N-substituted by alkylation methods, such as with a reactive ester as discussed above in the presence of base, for instance with a substituted alkyl halide with potassium carbonate. Alternatively, hydroxy alkylation can be accomplished by reaction with an alkylene oxide such as ethylene oxide, or alklation by N-acylation followed by reduction of the resulting amide, for instance by reduction with lithium aluminum hydride in tetrahydrofuran.

The foregoing is a general description of the main synthetic routes in the preparation of 10 - (ω - piperazinylalkyl) - 2 - perfluoroalkylpheothiazine derivatives. It will be readily apparent to one skilled in the art that variations of these procedures are possible. Of particular advantage as preparative procedures are the first two methods discussed, namely, substitution of 2 - perfluoroalkylphenothiazine in the 10-position of the nucleus by reaction with a reactive piperazinylalkyl ester, and utilization of 2 - perfluoroalkylphenothiazine derivatives substituted in the 10-position with aliphatic chains containing a reactive terminal group.

It will be readily apparent to one skilled in the art that certain of the compounds of this invention, notably those in A is represented by an aliphatic carbon chain branched so that an asymmetric carbon atom is formed or where the ω-piperazinyl moiety is C-substituted, may be present as optical or cis-trans isomers. The

connotation of the general formulae presented herein is to include the separated *d* or *l* optical isomers as well as the *dl* mixture of these isomers. If desired, the isomers may be separated for individual use by separation methods known to the art, such as fractional crystallization of the *d*-tartrate salts of the perfluoroalkylphenothiazine derivatives. Alternatively, a synthesis starting with an optically active side chain may yield the desired optical isomer.

The following examples will be illustrative of compounds of this invention and the procedures for their preparation and will serve to make fully apparent all of the compounds embraced by the general formula given above and the preparation thereof respectively.

EXAMPLE 1.

A suspension of 69.0 g. of 2 - trifluoromethylphenothiazine in 1 l. of toluene with 10.0 g. of sodium amide is heated at reflux with high speed stirring for 15 minutes. A solution of 54.1 g. of 1 - formyl - 4 - ($3^1$-chloropropyl) - piperazine, [prepared by formylating 1 - ($3^1$ - hydroxypropyl) - piperazine by refluxing in an excess of methyl formate, purifying the 1 - formyl - 4 - ($3^1$ - hydroxypropyl) - piperazine by vacuum distillation, reacting this compound with an excess of thionyl chloride at reflux and isolating the desired 1 - formyl - 4 - ($3^1$ - chloropropyl)-piperazine by neutralization with sodium carbonate solution followed by distillation] in 200 ml. of toluene is added. The reflux period is continued for four hours. The cooled reaction mixture is treated with 200 ml. of water. The organic layer is extracted twice with dilute hydrochloric acid. The acid extracts are made basic with ammonia and extracted with benzene. The volatiles are taken off *in vacuo* at the steam bath to leave a dark brown oil which is 10-[$3^1$-N-formylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine. It can be distilled at 260° C. at 10 microns, or used directly without distillation if desired.

EXAMPLE 2.

A solution of 33 g. of 10 - ($2^1$ - chloroethyl)-2 - trifluoromethylphenothiazine (prepared by the reaction of ethylene oxide with 2-trifluoromethylphenothiazine followed by subsequent treatment of the $\beta$ - hydroxyethyl compound with thionyl chloride) and 25 g. of anhydrous piperazine in 200 ml. of isoamyl alcohol is heated at reflux for twelve hours. The reaction mixture is then washed well with water. The organic layer is extracted with dilute hydrochloric acid. After neutralizing with ammonia and extracting with ethyl acetate, drying and evaporating the acetate extracts gives 5 g. of the crude base, 10 - ($2^1$ - piperazinylethyl) - 2 - trifluoromethylphenothiazine.

A suspension of 3.9 g. of 10 - ($2^1$ - piperazinylethyl) - 2 - trifluoromethylphenothiazine, 2.0 g. of 2 - bromo - 1 - diethylaminoethane and 0.5 g. of sodium amide in 50 ml. of benzene is heated at reflux with stirring for six hours. The reaction mixture is isolated by the procedure of Example 1. The crude syrup, 10 - [$2^1$ - ($\beta$ - N - diethylaminoethylpiperazinyl) - ethyl] - 2 - trifluoromethylphenothiazine, is purified by molecular distillation, at 195° C. at 1 micron.

EXAMPLE 3.

A solution of 24.0 g. of 10 - ($3^1$ - hydroxypropyl) - 2 - trifluoromethylphenothiazine *p*-toluene sulfonate, (prepared by reacting 2 - trifluoromethylphenothiazine with $\gamma$ - bromopropyltetrahydropyranyl ether, removing the protective group with mineral acid and acylating with tosyl chloride in pyridine), 20.0 g. of N-hydroxyethoxyethylpiperazine in 300 ml. of ethanol with 10.0 g. of potassium carbonate is heated for six hours with stirring. The solution is diluted with water, evaporated *in vacuo* and extracted with ethyl acetate. The dried oragnic extract is evaporated to leave a crude syrup of 10 - [$3^1$ - N - hydroxyethoxyethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

EXAMPLE 4.

Heptafluoropropylbenzene (180 g.) is slowly added to a mixture of nitric acid (d. 1.5) and concentrated sulfuric acid while maintaining the temperature at 20—30° C. The reaction mixture is quenched in an ice slurry, taken up in benzene and dried. Distillation at 100° C. at 10 mm. gives 1 - heptafluoropropyl - 3 -nitrobenzene. A mixture of 125 g. of this compound in 300 ml. of purified dioxane is reduced with hydrogen at 2,000 p.s.i. in the presence of 15 g. of Raney nickel catalyst. Dilution with benzene, filtering the catalyst and evaporation gives a residue 3-heptafluoropropylaniline, b.p. 95 to 96° C., at 12 mm.

Equivalent amounts of potassium carbonate, 2-chlorobenzoic acid and the anile with 5.0 g. of copper powder in 500 ml. of amyl alcohol are heated at reflux with stirring for 24 hours. The basic reaction mixture is subjected to steam distillation. The residue is an aqueous slurry of the desired product as the sodium salt, 2-($3^1$ - heptafluoropropylphenylamino) - benzoic acid. The free acid is obtained by trituration with excess dilute hydrochloric acid.

The water-washed aminobenzoic acid (225 g.) is decarboxylated by heating at 200° C. until the evolution of carbon dioxide ceases. A mixture of 33.5 g. of the resulting crude solid, 3 - heptafluoropropyldiphenylamine, and 17.4 g. of sulfur and 0.3 g. of iodine is heated at 160—180° C. until the evolution of hydrogen sulfide ceases. The reaction mass is then extracted with hot benzene. Concentration and cooling separates greenish yellow platelets of 2 - heptafluoropropylphenothiazine.

A suspension of 20.0 g. of 2-heptafluoropropylphenothiazine, 12.0 g. of 3-chloro-1-(N - hydroxyethylpiperazinyl) - propane and 3 g. of potassium carbonate in 300 ml. of toluene is heated at reflux for four hours. After

working up the mixture as in Example 1, a viscous syrup, 2 - heptafluoropropyl - 10 - [3¹-(N - hydroxyethylpiperazinyl) - propyl]-phenothiazine, is obtained by molecular distillation.

A solution of 2.0 g. of this base in 25 ml. of ethyl acetate is reacted with a slight excess of maleic acid in ethyl acetate. Concentration and cooling gives the dimaleate salt.

EXAMPLE 5.

A solution of 103.5 g. of 10-[3¹-(N-formylpiperazinyl - propyl] - 2 - trifluoromethylphenothiazine (made as in Example 1) in 400 ml. of ethanol and 218 ml. of water containing 26 ml. of 40% sodium hydroxide solution is heated at reflux for two hours. The alcohol is taken off *in vacuo* on the steam bath. The residue is swirled with benzene and water. The dried benzene layer is evaporated *in vacuo*. The residue is vacuum distilled to give a viscous, yellow oil, 10-(3¹-piperazinyl - propyl) - 2 - trifluoromethylphenothiazine, distilling at 210—235° C. at 0.5 to 0.6 mm. A suspension of 7.8 g. of 10-(3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (made in the above manner), 3.4 g. of ω-bromobutanol and 8.0 g. of potassium carbonate in 150 ml. of xylene is heated at reflux with stirring for five hours. After working up the reaction mixture as in Example 4, and distilling the crude basic residue, a viscous syrup is obtained, 10 - [3¹ - (N - ω-hydroxybutylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

A solution of 1.1 g. of the base is dissolved in 25 ml. of pyridine and 0.5 ml. of butyryl chloride is added. After standing at room temperature for 12 hours, the reaction mixture is quenched. The separated product is washed well with water, dried *in vacuo* and taken up in ethyl acetate ether. Dry hydrogen chloride gas is passed through the solution to separate crystals of 10 - [3¹ - (N - ω - butyryloxybutylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dihydrochloride.

EXAMPLE 6.

A solution of 3.9 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (made as in Example 5), in 150 g. of benzene is swirled while 1.8 g. of phenylacetyl chloride is added dropwise. After standing overnight, the separated crystals of 10 - [3¹ - (N - phenylacetylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine hydrochloride are removed by filtration and washed with ether.

EXAMPLE 7.

A solution of 3.8 g. of 10 - (2¹ - piperazinylethyl) - 2 - trifluoromethylphenothiazine (made as in Example 2) in 150 g. of benzene with 4 ml. of pyridine is swirled while 3 ml. of acetic anhydride are added. The reaction mixture is allowed to stand overnight and evaporated to dryness. The residue after the usual acid extraction and neutralization, is taken up in ethyl acetate and reacted with one equivalent of maleic acid to give 10 - [2¹ - (N-acetylpiperazinyl) - ethyl] - 2 - trifluoromethylphenothiazine maleate.

EXAMPLE 8.

A solution of 8.6 g. of 10-[3¹-(N-hydroxyethylpiperazinyl)propyl] - 2 - trifluoromethylphenothiazine in 50 g. of pyridine is swirled as 3.0 g. of benzoyl chloride is added. The reaction mixture, after standing for eight hours, is poured into a large volume of water. The material which separates is washed well with water, taken up in ether, and treated with ethereal hydrogen chloride to give crystals of 10 - [3¹ - (N - benzoyloxyethylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine dihydrochloride; melting point 226—228° C.

EXAMPLE 9.

A suspension of 26.7 g. of 2 - trifluoromethylphenothiazine, 25.0 g. of N-carbethoxy-N¹ - (γ - chloro - β - methylpropyl) - piperazine, prepared by condensing N - carbethoxypiperazine with 3 - bromo - 2 - methylpropylchloride, and 4.5 g. of sodium amide in 500 ml. of toluene is reacted and worked up following the procedure of Example 1 to leave a dark oil, 10 - [3¹ - (N - carbethoxypiperazinyl)-2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine.

EXAMPLE 10.

A solution of 28.4 g. of 10 - [3¹ - (N-carbethoxypiperazinyl) - 2¹ - methylpropyl]-2 - trifluoromethylphenothiazine (made as in Example 9) in 300 ml. of aqueous ethanol and 15 ml. of 40% sodium hydroxide solution is heated at reflux for four hours. The alcohol is removed *in vacuo* and the residue is swirled with benezene and water. The dried benzene layer is evaporated. The thick residue is distilled to give a viscous, yellow, oil, 10-(2¹-methyl - 3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine, b.p. 210—215° C. at 0.1 mm. which solidifies upon standing.

A portion of this base, 2.9 g., is dissolved in 75 ml. of ethyl acetate and reacted with 3g. of mandelic acid in 50 ml. of ethanol. The mixture is allowed to evaporate on the steam bath until the salt begins to separate. Cooling yields 10 - (2¹ - methyl - 3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine dimandelate.

A second portion of the base, 2.9 g., is dissolved in 75 ml. of ethyl acetate and mixed with 5 ml. of alcoholic hydrogen bromide. Cooling gives the dihydrobromide salt of the base.

A solution of 5.7 g. of 10 - (2¹ - methyl-3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine, in 150 ml. of ethanol is warmed with 1.7 g. of ethylene oxide to 50° C. for one hour. The volatiles are removed *in vacuo* to leave 10 - [3¹ - (N - hydroxyethylpiperazinyl) - 2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine.

A solution of 1.6 g. of the hydroxyethyl base in 50 ml. of ether-benzene is heated at

reflux with 1 ml. of acetyl chloride. The separated monohydrochloride of 10 - [3¹ - (N-acetoxyethylpiperazinyl) - 2¹ - methylpropyl]-2 - trifluoromethylphenothiazine is optionally isolated as such or shaken in an ethyl acetate-sodium carbonate solution mixture and converted to the dimaleate salt with an excess of maleic acid.

A solution of 1.6 g. of the hydroxyethyl base in 50 ml. of ether-benzene is heated at reflux with 0.8 g. of benzoyl chloride. The hydrochloride of 10 - [3¹ - (N - benzoyloxyethylpiperazinyl) - 2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine is isolated as described above.

EXAMPLE 11.

A solution of 2.7 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (made as in Example 5) and 1.5 g. of benzoyl chloride in 125 ml. of benzene is heated at reflux for several hours. Concentration and standing yields crystals of the hydrochloride of 10 - [3¹ - (N - benzoylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

Another aliquot containing 2.7 g. of the base and 1.2 g. of 2-furoyl chloride is reacted and worked up as above to yield 10 - [3¹ - (N-furoylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine hydrochloride.

EXAMPLE 12.

A suspension of 36.7 g. of 2-heptafluoropropylphenothiazine (made as in Example 4), 4.0 g. of sodium amide and 27.5 g. of N-diethylcarbamyl - N¹ - (γ - chloropropyl)-piperazine (prepared by reacting N - diethylcarbamylpiperazine with γ - chloropropyl bromide in xylene with sodium amide in 300 ml. of toluene is heated at reflux for six hour. The reaction mixture is worked up following the procedure of Example I, but the hydrochloride salt is recovered and purified by crystallization to give 10 - [3¹ - (N - diethylcarbamylpiperazinyl) - propyl] - 2 - heptafluoropropylphenothiazine hydrochloride.

EXAMPLE 13.

A solution of 53.0 g. of crude 10 - [3¹ - (N-diethylcarbamylpiperazinyl) - propyl] - 2-heptafluoropropylphenothiazine hydrochloride (made as in Example 12) in 200 ml. of concentrated hydrochloric acid is heated at reflux for 10 hours. The solution is diluted with water and filtered. The filtrate is neutralized with 40% sodium hydroxide solution. The separated product is taken up in chloroform, dried and treated with hydrogen chloride gas to separate 2 - heptafluoropropyl - 10 - (3¹ piperazinylpropyl) - phenothiazine dihydrochloride.

A suspension of 5.8 g. of this salt in 50 ml. of toluene with 1.8 g. of β-bromoethyl acetate and 2.0 g. of potassium carbonate is heated at reflux, with stirring, for 12 hours. Water is added to the cooled mixture. The resulting organic layer is extracted into dilute hydrochloric acid. After neutralizing the extracts and taking the separated base up in benzene, a residue is obtained by evaporating the organic solvent *in vacuo*. This residue is chromatographed on alumina. The purified fraction of 10 - [3¹ - (N - acetoxyethylpiperazinyl)-propyl] - 2 - heptafluoropropylphenothiazine dihydrochloride is taken up in ethyl acetate and mixed with alcoholic hydrogen chloride. Concentration *in vacuo* enables crystals of the dihydrochloride salt to be recovered.

EXAMPLE 14.

A suspension of 2.6 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (made as in Example 5), 0. 5 g. of sodium amide and 1.4 g. of 4 - chloro - 1 - dimethylaminobutane in 50 ml. of toluene is heated at reflux for 24 hours. After working up as in Example I, the viscous base, 10 - [3¹ - (N-dimethylaminobutylpiperazinyl) - propyl] - 2-trifluoromethylphenothiazine is recovered.

A solution of 1.0 g. of this base in 50 ml. of ethanol is treated with 0.6 g. of methanesulfonic acid. Trituration with ether and cooling gives the trimethanesulphonate salt.

EXAMPLE 15.

A suspension of 8.0 g. of 10 - (2¹ - piperazinylethyl) - 2 - trifluoromethylphenothiazine, 1.8 g. of potassium carbonate and 1.6 g. of allyl chloride in 100 ml. of aqueous ethanol is stirred at reflux for three hours. After working up as described in Example 13, crystals of 10 - [2¹ - (N - allylpiperazinyl) - ethyl]-2 - trifluoromethylphenothiazine dihydrochloride are obtained.

EXAMPLE 16.

A suspension of 13.4 g. of 2-trifluoromethylphenothiazine, 2.1 g. of sodium amide and 12.5 g. of 3 - chloro - 1 - (N - phenylpiperazinyl) - propane in 250 ml. of toluene is heated at reflux for eight hours. After working up as described in Example 1, crystals of 10 - [3¹ - (N - phenylpiperazinyl) - propyl]-2 - trifluoromethylphenothiazine maleate are recovered.

EXAMPLE 17.

A suspension of 26.7 g. of 2 - trifluoromethylphenothiazine in 600 ml. of toluene with 4.5 g. of sodium amide is heated at reflux and then reacted for six hours with 35.2 g. of 4-carbobenzoxy - 1 - (ω - chloropropyl) - 2,5-diethylpiperazine, prepared by reacting N-carbobenzoxy - 2,5 - diethylpiperazine with γ-chloropropyl bromide in benzene with sodium amide. The reaction mixture containing 10-[3¹ - N - carbobenzoxy - 2¹¹,5¹¹ - diethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine is washed with water and treated with dilute hydrochloric acid. The acid extracts are warmed briefly, cooled and treated with sodium hydroxide solution. The separated base is taken up in ethyl acetate, dried and micromolecularly distilled to give the thick base, 10 - [3¹ - (2¹¹,5¹¹ - diethylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

A solution of 3.2 g. of the base in 75 ml. of benzene is heated at reflux with 1.2 g. of isocrotonyl chloride with sodium carbonate for several hours. The reaction mixture is treated with dilute hydrochloric acid after neutralization. The product is taken up in ethyl acetate, dried and reacted with maleic acid to give 10-[3¹ - (N - isocrotonyl - 2¹¹,5¹¹ diethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dimaleate.

Another solution of 3.2 g. of the base in 75 ml. of benzene is reacted with 1.5 g. of dichloroacetyl chloride as above to give the monohydrochloride salt of 10 - [3¹ - (N - dichloroacetyl - 2¹,5¹ - diethylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

EXAMPLE 18.

A suspension of 2.7 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (Example 5) in 50 ml. of dimethyl formamide with 1.0 g. of potassium carbonate is stirred while 1.3 g. of benzyl chloride is added. The solution is heated at 80° C. for four hours and poured into an excess of water. The resulting precipitate is washed and extracted into benzene. An excess of hydrogen chloride in ethyl acetate gives 10 - [3¹ - (N - benzylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dihydrochloride.

Another portion of 2.7 g. of the base is reacted with 1.9 g. of phenethyl bromide, as above, to give 10 - [3¹ - (N - phenethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dihydrochloride.

Another portion (2.7 g.) is alkylated with 2.2 g. of ω - phenylbutyl bromide to give the N - ω - phenylbutyl analogue.

The base (5.4 g.) is alkylated with 2.6 g. of thenyl chloride as above. The dimaleate salt of 10 - [3¹ - (N - thenylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine is obtained by reacting the crude base with an excess of maleic acid in ethyl acetate solution.

EXAMPLE 19.

A solution of 2.8 g. of 10 - (2¹ - methyl-3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (Example 10) and 1.6 g. of cyclopentylpropionyl chloride in 50 ml. of benzene is heated at reflux for three hours. The solid separates to give crystals of 10 - [3¹-(N - cyclopentylpropionylpiperazinyl) - 2¹ methylpropyl] - 2 - trifluoromethylphenothiazine hydrochloride.

Another solution of 2.8 g. of the base is reacted with 1.5 g. of hexahydrobenzoyl chloride, as above, to give the hydrochloride of 10 - [3¹ - (N - hexahydrobenzoylpiperazinyl)-2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine.

The base (2.8 g.) is reacted with 2.0 g. of β-cyclohexylethyl bromide in dimethylformamide and 1.0 g. of potassium carbonate is reacted and the product isolated as described in Example 13, to give the dimaleate salt of 10 - [3¹ - (N - cyclohexylethylpiperazinyl)-2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine.

EXAMPLE 20.

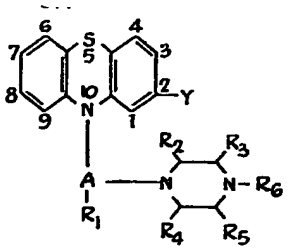
A solution of 3.4 g. of 10 - [3¹ - (N-hydroxybutylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine (Example 5) in 25 ml. of benzene is reacted with 2.3 g. of furoyl chloride in 25 ml. of benzene at reflux for two hours. The hydrochloride of 10 - [3¹-(N - furoyloxybutylpiperazinyl) - propyl] - 2-trifluoromethylphenothiazine separates as a crystalline solid.

EXAMPLE 21.

A suspension of 15.4 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine in 7.5 ml. of concentrated hydrochloric acid and 100 ml. of water is heated to 85° C. The volume of the reaction mixture is brought to 500 ml. with water. Ethanol (100 ml.) is added along with 3.6 g. of potassium cyanate in 25 ml. of water. After refluxing for one hour, the solvent is removed. The cooled reaction mixture is neutralized with ammonium hydroxide. The suspension is extracted with chloroform. The dried chloroform extract is evaporated to leave crystals of 10 - [3¹ - (N-carbamylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

WHAT WE CLAIM IS:—

1. Chemical compounds of the class consisting of a free base and its nontoxic acid addition salts, the free base having the formula:



in which Y is perfluoroalkyl of 1 to 3 carbon atoms; A is an alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms; $R_1$ is H, $R_2$, $R_3$, $R_4$ and $R_5$ are methyl, ethyl or hydrogen; $R_6$ is cycloalkyl having 5 or 6 carbon atoms, cycloalkylalkyl having 6 to 10 carbon atoms, alkenyl having 2 to 6 carbon atoms, dialkylamino - lower - alkyl having 1 to 6 carbon atoms in each of the alkyl portions and 2 to 6 carbon atoms in the lower alkyl portion, hydroxy - lower - alkyl having 2 to 6 carbon atoms in the alkyl portion, hydroxy - lower - alkyl - oxy - lower - alkyl, the lower alkyl portions having 2 to 6 carbon atoms, phenyl, cinnamyl, furoyloxybutyl, furoyl, thenyl, monocyclic aralkyl having 2 to 6 carbon atoms in the alkyl portion, aliphatic acyl having 1 to 6 carbon atoms, alicyclic aliphatic acyl having 7 to 10 carbon atoms,

monocyclic aryl-aliphatic acyl having 6 to 10 carbon atoms, carbomethoxy, carbethoxy, carbobenzoxy, carbamyl, dialkyl carbamyl having 1 to 6 carbon atoms in the alkyl portions and N-phenyl carbamyl, aliphatic acyloxy-lower-alkyl having 1 to 6 carbon atoms in the acyloxyportion and 2 to 6 carbon atoms in the lower alkyl portion, or monocyclic aroyloxy-lower alkyl having 2 to 6 carbon atoms in the lower alkyl portion, the values of Y, A, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$ and $R_6$ being chosen so that in any one compound, when Y is $CF_3$, A is propylene and $R_1$, $R_2$, $R_3$, $R_4$ and $R_5$ are each hydrogen, $R_6$ is not hydroxy-lower-alkyl having 2 or 3 carbon atoms in the alkyl portion, nor aliphatic acyloxy - lower - alkyl having 1 to 6 carbon atoms in the acyloxy portion and 2 or 3 carbon atoms in the lower alkyl portion.

2. 10 - [$3^1$ - (N - Hydroxyethoxyethyl-piperazinyl) - propyl] - 2 - trifluoromethyl-phenothiazine.

3. 10 - [$3^1$ - (N - Formylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

4. 2 - Heptafluoropropyl - 10 - [$3^1$ - (N-hydroxyethylpiperazinyl) - propyl] - phenothiazine.

5. 10 - [$3^1$ - (N - Carbamylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

6. 10 - [$3^1$ - (N - Hydroxyethylpiperazinyl)-$2^1$ - methylpropyl] - 2 - trifluoromethylphenothiazine.

7. 10 - [$3^1$ - (N - Acetoxyethylpiperazinyl)-$2^1$ - methylpropyl] - 2- trifluoromethylphenothiazine.

8. 10 - (Piperazinylalkyl) - perfluoroalkyl-phenothiazine derivatives as defined in Claim 1 when produced in accordance with any of Examples 1 to 21.

9. Process for the preparation of 10 - (piperazinylalkyl) - perfluoroalkylphenothiazine derivatives as defined in Claim 1 substantially as hereinbefore described with reference to any of Examples 1 to 21.

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Reference has been directed, in pursuance of Section 8 of the Patents Act, 1949 to specification No. 857,547 and reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949 to Patent No. 833,474.

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